PATENT SPECIFICATION

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COMPLETE SPECIFICATION

Improvements in or relating to the Production of Protoanemonin

We, OLIN MATHIESON CHEMICAL CORPORATION, a corporation organised under the laws of the State of Virginia, United States of America, or Ten Light Street, Baltimore 3, Maryland, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to the production of protoanemonin.

It is known from the work of Asahina *et al* (see Chemical Abstracts *14*, 1384') that levulinic acid may be brominated to beta-bromolevulinic acid which in turn may be acetylated with acetic anhydride to close the lactone ring and form 4-acetoxy-3-bromo-4-hydroxyvaleric acid-gamma lactone. Treatment of this lactone with anhydrous sodium acetate in boiling ether removes hydrogen bromide forming 4-acetoxy-4-hydroxy-2-pentenoic acid-gamma-lactone. Distillation of this bromine-free product effects removal of acetic acid and formation of protoanemonin.

It is also known that a similar treatment, i.e. with anhydrous sodium acetate in ether, of 3,4-dibromo-4-hydroxyvaleric acid-gamma-lactone results in the formation of 4-acetoxy-4-hydroxy-2-pentenoic acid-gamma-lactone which may be converted into protoanemonin as described above.

Protoanemonin is a strongly vesicant compound which is a highly reactive diene useful for the preparation of polymers and copolymers. Its dimer, known as anemonin, is of interest in the pharmaceutical art.

The yields of protoanemonin by the previously known methods of preparation are very poor. Indeed, the yields of the prior art processes have been so low that the product has been difficult, if not impossible, to obtain in any substantial amounts.

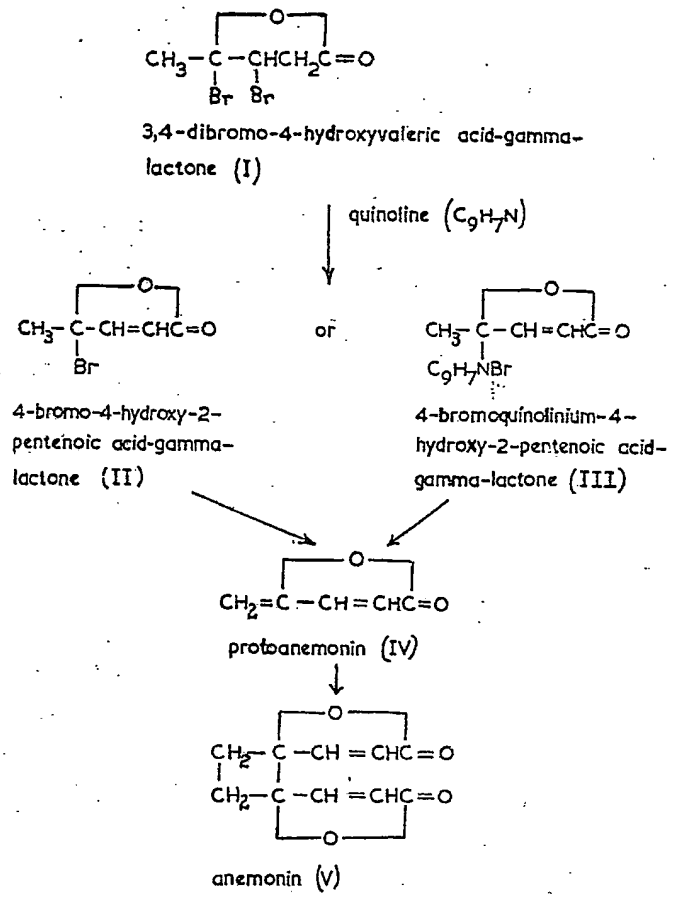
It is an object of the present invention to provide means for obtaining protoanemonin in greatly improved yields. It is a further object of the present invention to provide means for obtaining high yields of protoanemonin easily by a commercially practical process.

According to the present invention, there is provided a process of preparing protoanemonin, which comprises heating a solution of 3,4-dibromo-4-hydroxy-valeric acid-gamma-lactone in an inert solvent in the presence of a tertiary nitrogen base, and then distilling the resulting monobromolactone-containing reaction mixture in the presence of a tertiary nitrogen base to obtain protoanemonin.

In carrying out the process of the present invention, 3,4-dibromo-4-hydroxy-valeric acid-gamma-lactone (I) is treated with a tertiary nitrogen base, preferably quinoline, in two stages. In the first stage the dibromo product is converted into 4-bromo-4-hydroxy-2-pentenoic acid-gamma-lactone (II) or its quaternary adduct with the tertiary nitrogen base, for example, 4-bromoquinolinium-4-hydroxy-2-pentenoic acid-gamma-lactone (III). In the second step the monobromo product (II or III or a mixture of the same) is converted into protoanemonin (IV).

In the first step, one molecule of hydrogen bromide is removed by heating or refluxing the dibromo product (I) with an excess of the tertiary nitrogen base in an inert organic solvent. Suitable solvents for this purpose include ethyl ether, benzene and carbon bisulphide. The proportion of solvent used is not critical and the temperature may range from 35 to 80°C. or more. When the quinoline and ether are used, the resulting quinoline hydrobromide is removed suitably by filtration and the ether distilled off. The residue containing excess quinoline is distilled under reduced pressure to obtain protoanemonin (IV). This monomer polymerizes readily to anemonin (V).

The process may be illustrated by the following formulae:



The following examples will serve to illustrate the invention.

EXAMPLE I

A solution of 45.6 grams (0.47 mole) of 4-hydroxy-3-pentenoic acid-gamma-lactone (α-angelicalactone) dissolved in an equal volume of carbon bisulphide was cooled in an ice-salt mixture while introducing 74.4 grams (0.47 mole) of bromine. The carbon bisulphide was removed under reduced pressure at room temperature yielding as the residue the desired 3,4-dibromo-4-hydroxyvaleric acid-gamma-lactone (I).

The dibromo product (I) obtained above was dissolved in 400 ml. of anhydrous ether to which was added 0.2 gram of hydroquinone. The mixture was cooled in ice and salt while 120.8 grams (0.94 mole) of anhydrous quinoline was added dropwise. The mixture was next allowed to warm to room temperature and stand overnight. It was then refluxed for about 30 minutes. The ether solution was decanted from the precipitated quinoline hydrobromide which was extracted three times with small portions of ether (50 to 100 ml.) each time refluxing for about 10 minutes. The washings were combined with the original solution and the ether was evaporated under reduced pressure at room temperature yielding as the residue 4-bromo-4-hydroxy-2-pentenoic acid-gamma-lactone (II) or its quaternary adduct, 4-bromoquinolinium - 4 - hydroxy - 2-pentenoic acid-gamma-lactone (III), or a mixture of the same in excess quinoline.

An additional 0.1 gram of hydroquinone was added to the mixture of the monobromo product obtained above and the mixture distilled under a pressure of 10—12 mm. of mercury, avoiding the introduction of atmospheric moisture. The crude protoanemonin (IV) with a boiling point of 76—86°C. at 10—12 mm. of mercury was obtained in high yield. It is strongly vesicant and polymerizes readily on standing at room temperature to the dimer, anemonin (IV).

EXAMPLE II

The procedure of Example I was repeated using benzene instead of ether as solvent. The yield of crude protoanemonin was 99.5% of theory.

EXAMPLE III

The procedure of Example I was repeated using ether as solvent and a mixture of picolines as the tertiary nitrogen base. The yield of crude protoanemonin was 72.8% of theory.

The procedure of Example I was also repeated using triethylamine, pyridine and sym.-collidine as the tertiary nitrogen base. Similar results, but somewhat lower yields, were obtained.

Although quinoline and other tertiary amine have previously been used for the abstraction of hydrogen bromide from organic bromine compounds, it has not been previously known that this could be accomplished where the bromine atom it attached to a carbon atom adjacent to an oxygen atom in the heterocyclic ring. Indeed, previous investigations indicated that it could not be done. For example, 2,3,4,6-tetra-acetyl-1-bromoglucose contains a very reactive bromine atom which easily undergoes substitution making this product a valuable intermediate in carbohydrate chemistry. However, treatment of this product, with the bromine atom on the carbon atom adjacent to the oxygen atom in the ring, with tertiary nitrogen bases yields the quaternary nitrogen compound rather than converting it to the desired unsaturated 0-heterocyclic compound. Trimethylamine behaves similarly. See Beilstein *2*, 148—149; Fischer *et al*, Ber. *43*, 1751 (1910); Karrer *et al*, Helv. Chim, Acta *4*, 817 (1921); *5*, 870 (1922); *7*, 519 (1924). The discovery that tertiary nitrogen bases would function as desired in the present invention with compounds having a bromine atom on a carbon atom adjacent to an oxygen atom in a heterocyclic ring could not be anticipated and in fact was unexpected.

The preferred inert organic solvents are of the low boiling point type such as ethyl ether, carbon bisulphide and benzene with boiling points of 35 to 80°C. The preferred tertiary nitrogen bases are of the relatively high boiling point type such as the tertiary aromatic nitrogen bases and particularly quinoline. Tertiary alkyl amines, e.g. tripropyl and tributyl amines, can be used as noted above but do not give as good yields as quinoline. With the preferred inert solvents and tertiary nitrogen bases the dibromo product (I) is readily converted to the monobromo product (II or III) by refluxing the solvent mixture containing excess tertiary nitrogen base. Then after removal of the solvent, the monobromo product is readily converted to protoanemonin by distilling in the presence of the excess base.

What we claim is:

1. A process of preparing protoanemonin, which comprises heating a solution of 3,4-dibromo-4-hydroxy-valeric acid-gamma-lactone in an inert solvent in the presence of a tertiary nitrogen base, and then distilling the resulting monobromolactone-containing reaction mixture in the presence of a tertiary nitrogen base to obtain protoanemonin.

2. A process of preparing protoanemonin, which comprises refluxing a solution of 3,4-dibromo-4-hydroxy-valeric acid-gamma-lactone in an inert solvent in the presence of a tertiary nitrogen base in excess, separating the solvent from the reaction mixture, and then distilling the reaction mixture comprising the resulting monobromolactone in the excess tertiary nitrogen base under reduced pressure to obtain protoanemonin.

3. A process according to claim 1 or 2, in which the tertiary nitrogen base is a tertiary aromatic nitrogen base such as quinoline or the picolines.

4. A process according to any of claims 1 to 3, in which the inert solvent has a boiling point in the range of 35—80° C.

5. A process according to claim 4, in which the inert solvent comprises ethyl ether, carbon bisulphide, or benzene.

6. A process according to claim 2, in which the tertiary nitrogen base comprises quinoline, and quinoline hydrobromide is separated from the reaction mixture before the latter is subjected to distillation.

7. A process according to any of the preceding claims, in which the distillation step is carried out in the absence of moisture.

8. A process of preparing protoanemonin in accordance with any of the preceding claims substantially as hereinbefore described.

9. Protoanemonin whenever prepared by the process according to any of claims 1 to 8.

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